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with the oligonucleotide of claim 1 under conditions such that the oligonucleotide hybridizes with mRNA encoding the heparanase so as to thereby inhibit the expression of the heparanase.--

A marked up copy of the amendments to the claims is attached hereto as **Exhibit A**.

REMARKS

Claims 1-7 and 9-28 are pending and under examination in the subject application. By this Amendment, applicant has amended claim 15, and canceled claims 21-27 without prejudice. Applicant maintains that the amendments to the claims raise no issue of new matter. Support for the amendments to claim 15 may be found in the specification as originally filed at, *inter alia*, page 2, line 12 to page 3, line 25; and at page 12, lines 25 to 27. Accordingly, applicant requests entry of this Amendment. After entry of this Amendment, claims 1-7, 9-20, and 28 will be pending and under examination.

Claims Rejected Under 35 U.S.C. §112 (first paragraph)

The Examiner stated that claims 15, 16, and 21-27 stand rejected, and claims 17-20 are newly rejected under 35 U.S.C. §112, first paragraph, because specification, while being enabling for antisense-mediated inhibition of heparanase expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of heparanase expression *in vivo*. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention commensurate in scope with these claims.

The Examiner stated that the invention is drawn to methods of inhibiting the expression of heparanase in a cell, which may be a cancer cell, comprising contacting said cell with antisense compositions that inhibit the expression of heparanase. The Examiner stated that the claims of the invention are also drawn methods of treating a subject having a condition associated with heparanase, wherein said compositions are administered to animals such that expression of heparanase is inhibited, wherein said condition may be cancer, which may be characterized by tumor metastasis, or involves reduction of angiogenesis, and to compounds comprising a carrier that may be a membrane permeable cationic reagent, or are effective to inhibit expression in a cell, or can pass through a cell membrane, wherein the language of said compound claim encompasses *in* vitro activity. The Examiner further stated that the specification teaches a method of using the claimed compositions to inhibit the expression of heparanase in T24 bladder carcinoma cell line, and that claims 17-20 are newly included in this rejection, because of functional language in said claims directed to methods of using the presently claimed compounds in cells encompassing *in vivo* applicability.

The Examiner also stated that applicant argues that M.P.E.P. §2164.03 requires only a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity for enablement, and that applicant's disclosure describing that antisense oligonucleotides have inhibited that transcript *in vitro* indicates that it can traverse the physical barriers mentioned in Braasch et al., and can thus be taken up with the

same efficiency by different cell types in order to be active in those cells. The Examiner stated that applicant points out that Agrawal teaches that antisense oligonucleotides can inhibit disease associated proteins, that the specificity of such methods has been verified in animal models, and that Tamm et al. teaches FDA approval of the therapeutic use of antisense oligonucleotides. The Examiner also stated that applicant argues that the problems of non-specific toxicity as delineated by Tamm et al. does not preclude activity or usefulness, that dosage issues can be resolved by routine experimentation, and assert that the previous Office Action did not cite reasons why the instantly claimed oligonucleotides would not have *in vivo* activity, and that the *in vivo* situation experimentation of the specification provides a reasonable correlation with the *in vivo* situation as exemplified in references provided by applicant. The Examiner stated that, finally, applicant perceives the enablement rejection of the previous Office action as requiring low toxicity, low immunogenicity, and a complete lack of harmful heparanase expression for patentability, and state that these are unreasonable demand upon applicant.

The Examiner further stated that applicant's arguments have been fully considered but they are not persuasive. The Examiner further stated that the five review articles cited in the previous Office action are considered to continue to demonstrate a high level of unpredictability in the development of therapeutic methods utilizing antisense oligonucleotides, and, furthermore, as exemplified in the aforementioned references, the in vitro exemplification is not considered to be adequately representative of the dynamic *in vivo* environment such that one skilled in the art would not readily be able to use the instant antisense oligonucleotides for *in vivo* use and to further provide

treatment without engaging in undue experimentation (see previous Office action for the precise reasons why). The Examiner also stated that while it is noted that some occurrences of success using antisense oligonucleotides *in vivo* do exist, the references previously cited clearly indicate that such occurrences do not represent the state of the art as a whole, and, further, success of one or even a few antisense studies is not generally representative of success as a whole for being able to design and deliver antisense oligonucleotides in vivo and further, for treatment.

The Examiner also stated that in arguing that applicant's antisense oligonucleotides of the disclosure are capable of inhibiting the transcript *in vitro*, which in turn indicates that said oligonucleotides can traverse the barriers mentioned Braasch et al., and further, that these oligonucleotides can thus be taken up as required by Agrawal, it is noted that the previous Office Action stated that applicant was enabled for such in vitro use, and that as it is applicant's position that this in vitro evidence provides enablement for the use of said oligonucleotides *in vivo*, it is pointed out that use of an *in vitro* model system does not recreate the complex extracellular milieu comprising the myriad of plasma and cell surface proteins that such oligonucleotides are expected to encounter, or re-create the immune response discussed in the prior Office Action, before ever reaching the target. The Examiner stated that, for these reasons, applicant's assertion that the instant oligonucleotides traverse cell membranes in a culture dish does not adequately correlate with the environment these oligonucleotides would encounter *in vivo*, and therefore does not suggest that the same will happen *in vivo*, and as mentioned in the previous Office Action and reiterated here, significant non-specific binding of

oligonucleotides, and particularly the phosphorothioated versions contemplated presently, are known in the art to bind problematically to unintended targets, causing experimental artifacts that can't be predicted from results obtained *in vitro*. The Examiner stated that applicant's specification does not provide any resolution to this art-recognized problem, in particular as it relates to targeting the instant gene and providing treatment by inhibiting it. The Examiner further stated that applicant states that the Examiner must provide reasons why the correlation between *in vitro* data on antisense compounds to *in vivo* effects is unpredictable, and that, in response, it is noted that the focus of these articles is the application of antisense compounds to *in vivo* effects is unpredictable. The Examiner further stated that it is noted that the focus of these articles is antisense-mediated inhibition *in vivo*, and further that this goal so far has been unattainable in any predictable fashion, and that this theme underlies all the literature cited in the previous Office Action. The Examiner stated that, for example, in Branch et al. on page 49, far right column, line 25-30, the subject of unpredictability is broached; "With so many possible sequences to choose from, and the likelihood that in vitro studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells.", Gewirtz et al. indicate (at page 3162, center column, 2nd to last paragraph) that studies of a transfection agent GS288 complexed with antisense oligonucleotides have been successful in a cell culture, but studies in primary cell lines are needed, and adds that "while the application of GS288 [a transfection agent] to cell culture experiments has been clearly demonstrated, its utility for therapeutic applications remains to be determined." The Examiner then stated that such language underscores the difficulties in moving from in vitro cell culture

experiments to the *in vivo* whole animal. The Examiner further stated that Agrawal et al. devotes the closing section on the unpredictabilities of *in vivo* efficacy, how moving from cell culture to the *in vivo* whole animal is an important hurdle where no reasonable degree of success can be assured, and that these passages all imply or explicitly state difficulty in attaining therapeutic success, and emphasize that such success has been elusive.

The Examiner stated that regarding applicant's assertion that the specificity of antisense methods has been verified in animal models, and that Tamm et al. teaches FDA approval for the therapeutic use of antisense oligonucleotides, it is reiterated that the intermittent occurrences of success using antisense oligonucleotides in vivo are considered to be outweighed by the failures and skepticism of researchers in the field. The Examiner further stated that for example, and as set forth previously, Braasch et al. states the major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology". The Examiner also stated that many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2), and "even when active oligomers are discovered, the difference than in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death." The Examiner stated that Branch confirms that "non-antisense effect are not currently predictable, rules for rational design cannot be applied to the production on non-antisense drugs, these effects must be explored on a case by case basis" and that Branch states in the abstract that the promise for antisense drug design is considerable, "However, they are far

more difficult to produce that was originally anticipated, and their ability to eliminate the function of a single gene has never been proven." The Examiner stated that when these references are viewed as a whole as required, it is apparent that applicant's arguments have wholly ignored the broad statements regarding the unpredictable state of the art of these authors, in favor of a piecemeal presentation of the infrequently noted successes. The Examiner stated that, for these reasons, the in vitro experimentation and prophetic guidance of the specification is not viewed as providing a reasonable correlation with the in vivo situation as exemplified in references above or, that the instantly claims oligonucleotide would actually have *in vivo* activity, and that furthermore, applicant only asserts that the problems of non-specific toxicity and dosage issues can be resolved by routine experimentation, but provide no evidence that these issues could ever be resolved routinely or without engaging in undue experimentation, particularly in view of the cited unpredictability in the art as described above and in the prior Office Action. The Examiner then stated that it is apparent for these reasons that one of skill in the art in attempting to practice the steps as recited in the claims would do so with no reasonable degree of certainty that treatment to any degree would be provided, and based on the lack of specific guidance in the disclosure as filed on how to deliver the instant antisense to the target in order to achieve some therapeutic effect in view of the known unpredictability in the art, the quantity of experimentation would thus require the de novo determination of a variety of factors needed to provide for the delivery and further treatment effects *in vivo*. The Examiner then stated that, as originally set forth, this is considered to require an undue amount of experimentation since the state of the art nor applicant's disclosure provide any specific guidance for

practicing the invention *in vivo* and or further for treatments as claimed.

The Examiner stated that, finally, the prior Office Action does not require applicant to provide formulations with low toxicity, low immunogenicity, and a complete lack of harmful heparanase expression for patentability, and that these issues were pointed out in an effort to point out the wide gap between the art-recognized problems of using nucleotide oligonucleotides in therapeutic treatments and the breadth of applicant's claims, and also the quantity of experimentation required to enable these broad claims. The Examiner stated that toxicity, immunogenicity, and targeting are all issues are all issues are not required to be fully resolved in order to be enabled, they are nevertheless real barriers towards the successful practice of such treatment methods, and remain unaddressed in any manner in applicant's disclosure. The Examiner stated that in summary, applicant's failure to disclose some facts or guidance leading one skilled in the art to be able, through reasonable experimentation, to provide any treatment other than by prophetic guidance makes it clear that the amount of experimentation required to attain successful therapeutic treatments of the type claimed by applicant that at least consider the art recognized issued of toxicity, immunogenicity, and targeting is prohibitively high.

In response, applicant traverses the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicant has hereinabove amended claim 15, and canceled claims 21-27 without prejudice. Applicant maintains that amended claim 15 is enabled by the specification as filed, as indicated by the Examiner in the March 11, 2003 Office Action. Accordingly, applicant requests

that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §103(a)

The Examiner stated that claims 1-6, 9-15, 17-20, and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kussie et al. (Biochem. Biophys. Res. Comm. 1999. 261: 183-187, applicant's IDS), in view of Pecker et al. (of record), Froehler et al. (of record), Taylor et al. (Drug Discov Today. 1999 Dec; 4(12):562-567, newly cited), and Baracchini et al. (U.S. Patent Number 5,801,154, newly cited). The Examiner stated that the invention of the above listed claims is drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase of SEQ ID NO: 18, wherein said oligo is 10-40 nucleotides long, contains at least on phophorothioate linkage, inhibits heparanase at least 50% as measured by western blot, wherein said oligo is made of DNA or RNA, or wherein said oligo is 15-25 nucleotides long, or is about 20 nucleotides long, or wherein said oligo comprises peptide-nucleic acid or morpholino linkages, or comprises internucleoside, sugar, or base modifications, or wherein said oligo is composed of 100% phosphorothioate linkages, or wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine, or wherein said modified sugar moiety is a 2'-O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof. The Examiner stated that Kussie et al. teach the sequence of a ribonucleic acid encoding a heparanase of SEQ ID NO:18. The Examiner stated that Kussie et

al. do not teach an antisense oligonucleotide that is 10-40 nucleotides long, contains at least one phosphorothioate linkage, inhibits heparanase at least 50% as measured by western blot, wherein said oligonucleotide is made of DNA or RNA, or wherein said oligonucleotide is 15-25 nucleotides long, or is about 20 nucleotides long, or wherein said oligonucleotide comprises peptide-nucleic acid or morpholino linkages, or comprises internucleoside, sugar, or base modifications, or wherein said oligonucleotide is composed of 100% phosphorothioate linkages, or wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine, or wherein said modified sugar moiety is a 2'-O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligonucleotide is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof. The Examiner also stated that Pecker et al. teaches an antisense oligonucleotide to heparanase, albeit a different heparanase transcript than that which encodes the instantly contemplated SEQ ID NO:18, wherein said antisense molecule contains at least one phosphorothioate linkage, wherein said oligonucleotide is made of DNA or RNA, or wherein said oligonucleotide is more preferably 19-25 nucleotides long, which may comprise peptide-nucleic acid or morpholino linkages, and may comprise internucleoside, sugar, or base modifications, wherein said modified sugar moiety may be a 2'- O-alkyl moiety, or wherein said target is human heparanase, or wherein said oligonucleotide is in a composition comprising a carrier, or wherein the oligonucleotide inhibits expression of heparanase, and methods of use thereof.

The Examiner also stated that Taylor et al. teaches that with

available bioformatics programs, one only needs to screen 3-6 oligomers per target in order to find one that can inhibit a gene with 66-95% efficiency. The Examiner further stated that Froehler et al. teaches 5-propynyl pyrimidine modifications of oligonucleotide nucleobases. The Examiner stated that Baracchini et al. teach using inhibitory antisense oligonucleotides in combination with carriers capable of passing through the cell membrane, wherein said carrier is a membrane permeable cationic reagent, wherein said carrier is lipofectin. The Examiner also stated that it would have been obvious for one of ordinary skill in the art to use the heparanase sequence of Kussie et al., which encodes the amino acid sequence of SEQ ID NO:18, and make antisense oligonucleotides targeted to heparanase as taught by Pecker et al., and, furthermore, it would have been obvious to incorporate 5-propynyl pyrimidine modifications into said antisense oligonucleotides as taught by Froehler et al., and to provide carriers for said compounds to traverse the cell membrane as taught by Baracchini et al. The Examiner further stated that one would have been motivated to make such antisense oligonucleotides, because Pecker et al. have already made such oligonucleotides targeting a closely related heparanase sequence, and because Pecker et al. further teach that chemical inhibitors of heparanase inhibited lung metastases induced by B16 melanoma, Lewis lung carcinoma and mammary adenocarcinoma cells. The Examiner stated that, thus, one of ordinary skill would have been motivated to find alternate inhibitors of heparanases so as to inhibit cancer, such as the instantly claimed antisense sequences targeting the heparanase of SEQ ID NO:18., and, furthermore one of ordinary skill in the would have been motivated to modify such sequences as taught by Froehler et al., because the oligonucleotides of Pecker et al. have already modified in order to confer nuclease resistance and enhance cellular entry, and

because Froehler et al. teach that such 5-propnyl pyrimidine modification, enhance binding of the antisense oligonucleotide to the target gene, and also enhance cellular entry, which are key steps in the mechanism of antisense oligo-mediated inhibition. The Examiner stated that, finally, one would have motivated to combine the instantly contemplated oligonucleotides with carrier that enhance cellular entry as taught by Baracchini et al., because Pecker et al. taught carriers that confer enhanced cellular entry, and because Baracchini also indicates that lipofectin enhances cellular entry. The Examiner then stated that one of ordinary skill in the art would have had a responsible expectation of success of making such antisense oligonucleotides, because Pecker et al. already teach antisense oligonucleotides directed to a different heparanase transcript, and because Kussie et al. teach the instantly contemplated heparanase transcript of SEQ ID NO:18, and that one of ordinary skill could have easily made antisense oligonucleotides targeting Kussie's sequence since Pecker, et al. teach such targeting to other heparanase sequences, and because Taylor et al. points out that with available bioinformatics programs, one only needs to screen 3-6 oligomers per target in order to find one that can inhibit a gene with 66-95% efficiency. The Examiner stated that one of ordinary skill would have had a reasonable expectation of success in incorporating the modifications of Froehler et al. into such antisense oligonucleotides, and also to combining antisense compounds with cationic carriers as taught by Baracchini et al., because both Froehler et al. and Baracchini et al. provide detailed instructions on their synthesis, and because such modifications and combinations are routinely performed by those of ordinary skill in the art.

The Examiner stated that, finally, applicant has argued that the

functional language in claim 1 whereby inhibition of the target is verified by western blot should be included as a claim limitation rather than being considered functional language which has no bearing on patentability. The Examiner stated that in response to this argument, applicant is referred to the reference of Taylor et al. provided above, wherein it is stated that using available tools, it is within the capacity of one of ordinary skill in the art to synthesize antisense compounds with greater than 50% inhibitory capability with a reasonable amount of experimentation. The Examiner stated that the western blot limitation of the claims is considered to be no more than an intended use/functional limitation associated with what is actually a compound being claimed, and that it is not readily apparent from claim 1, the specification, applicant's argument or otherwise, that such intended use recitation breathes any new significant or special property to what is otherwise a simple antisense oligonucleotide that would have been obvious in view of the collective art cited, and that thus the western blot teaching of the claims is not considered to further distinguish what are considered to be obvious antisense compounds as claimed. The Examiner also stated that that claims 17-20 are included in this rejection under 35 U.S.C. §103(a), even thought the pharmaceutical language of said claims implies *in vivo* applicability and which intended use has been addressed under 35 U.S.C. §112 1st paragraph enablement because prior art purposes, intended use limitations for claimed compositions rarely breath life and meaning, and thus rarely provide patentable distinction, into what otherwise are known compositions and that such is the present case. The Examiner stated that claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent upon a rejected base claim, but would allowable if rewritten in independent from including

all of the limitations of the base claim and any intervening claims. The Examiner finally stated that a sequence search performed against the oligonucleotides of SEQ ID NO.s: 3, 4, and 5 indicated no anticipating prior art, and, thus the oligonucleotides of the independent SEQ ID NO.s recited in claim 7 are considered free of the art if rewritten in independent form and including all of the limitations of claim 1.

In response, applicant traverses the Examiner's rejection. Applicant maintains that the cited references do not teach all the elements of the claimed invention. Specifically, applicant notes that Kussie et al. does not teach SEQ ID NO:18. For example, amino acid residue number fourteen (14) of the sequence taught in Kussie et al. is different from the corresponding residue number in SEQ ID NO:18. Moreover, the remaining references cited by the Examiner do not cure this deficiency.

In addition, applicant maintains that Taylor et al. merely asserts a method of obtaining an active antisense in a very general sense, but does not detail or explain how to obtain an active antisense molecule, does not explain what the "bioinformatic program" is, and, furthermore, states that such data is unpublished (see pages 564-565 of Taylor et al.). Applicant maintains that one of ordinary skill in the art could have not combined the Taylor's description with his own knowledge to make the claimed invention as the reference provides no examples and no guidance how to achieve such. Taylor et al. is not an enabling reference, and, moreover, the other references cited by the Examiner do not cure this deficiency.

Applicant thus maintains that the cited references fail to support a *prima facie* case of obviousness. Accordingly, applicant

respectfully requests that the Examiner reconsider and withdraw this ground of the rejection.

Third Supplemental Information Disclosure Statement

In accordance with his duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the following reference which is listed on the attached Form PTO-1449 (**Exhibit B**) and attached hereto as **Exhibit C**:

1. Dempsey, L.A. et al., Heparanase expression in invasive trophoblasts and acute vascular damage, *Glycobiology* 10(5) 467-475 (2000).

This Third Supplemental Information Disclosure Statement supplements the Second Supplemental Information Disclosure Statement filed December 27, 2002, the Supplemental Information Disclosure Statement filed June 25, 2002, and the Information Disclosure Statement filed March 4, 2002 by applicant in connection with the above-identified application.

This Third Supplemental Information Disclosure Statement is submitted under 37 C.F.R. §1.97(c). Accordingly, applicant encloses a check for ONE HUNDRED AND EIGHTY DOLLARS ($180.00) pursuant to 37 C.F.R. §1.17(p).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $180.00 fee for submission of an Information Disclosure Statement under 37 C.F.R. §1.97(c), is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

6/11/03
John P. White Date
Reg. No. 28,678